The Crux

BIMONTHLY FORUM FOR THE LABORATORIANS

CONTENTS

Editorial

Hyperthyroidism is the condition that occurs due to excessive production of thyroid hormone by the thyroid gland. **Thyrotoxicosis** is the condition that occurs due to excessive thyroid hormone of any cause and therefore includes hyperthyroidism. Some, however, use the terms interchangeably. Signs and symptoms vary between people and may include irritability, muscle weakness, sleeping problems, a fast heartbeat, poor tolerance of heat, diarrhea, enlargement of the thyroid, and weight loss. Symptoms are typically less in the old and during pregnancy. An uncommon complication is thyroid storm in which an event such as an infection results in worsening symptoms such as confusion and a high temperature and often results in death. The opposite is hypothyroidism, when the thyroid gland does not make enough thyroid hormone.

Graves' disease is the cause of about 50% to 80% of the cases of hyperthyroidism internationally. Other causes include multinodular goiter, toxic adenoma, inflammation of the thyroid, eating too much iodine, and too much synthetic thyroid hormone. A less common cause is a pituitary adenoma. The diagnosis may be suspected based on signs and symptoms and then confirmed with blood tests. Typically blood tests show a low thyroid stimulating hormone (TSH) and raised T_3 or T_4. Radioiodine uptake by the thyroid, thyroid scan, and TSI antibodies may help determine the cause.

Treatment depends partly on the cause and severity of disease. There are three main treatment options: radioiodine therapy, medications, and thyroid surgery. Radioiodine therapy involves taking iodine-131 by mouth which is then concentrated in and destroys the thyroid over weeks to months. The resulting hypothyroidism is treated with synthetic thyroid hormone. Medications such as beta blockers may control the symptoms and anti-thyroid medications such as methimazole may temporarily help people while other treatments are having effect. Surgery to remove the thyroid is another option. This may be used in those with very large thyroids or when cancer is a concern. It occurs between two and ten times more often in women. Onset is commonly between 20 and 50 years of age. Overall the disease is more common in those over the age of 60 years. The **DISEASE DIAGNOSIS** space this month is occupied by Hyperthyroidism.

Additionally, **INTERPRETATION** as well as **TROUBLE SHOOTING** too is devoted to Thyroid also. Happy reading.

DISEASE DIAGNOSIS

HYPERTHYROIDISM

Background

Hyperthyroidism is a set of disorders that involve excess synthesis and secretion of thyroid hormones by the thyroid gland. The resulting elevation in levels of free thyroxine (FT_4), free triiodothyronine (FT_3), or both leads to the hypermetabolic condition of thyrotoxicosis. Thus, although many clinicians (endocrinologists excluded) use the terms hyperthyroidism and thyrotoxicosis interchangeably, the 2 words have distinct meanings. For example, both exogenous thyroid hormone intake and subacute thyroiditis can cause thyrotoxicosis, but neither constitutes hyperthyroidism, because the conditions are not associated with new hormone production. The most common forms of hyperthyroidism include diffuse toxic goiter (Graves disease), toxic multinodular goiter (Plummer disease), and toxic adenoma. Together with subacute thyroiditis, these conditions constitute 85-90% of all causes of thyrotoxicosis. The most reliable screening measure of thyroid function in the healthy ambulatory adult population is the TSH level. The degree of thyrotoxicosis is determined by measurement of thyroid hormone levels. Autoantibody testing, and nuclear thyroid scintigraphy in some cases, can provide useful etiologic information. Treatment of hyperthyroidism includes symptom relief, as well as therapy with antithyroid medications, radioactive iodine, or thyroidectomy. However, antithyroid medications are not effective in thyrotoxicosis from subacute thyroiditis, because these cases result from release of preformed thyroid hormone.

Pathophysiology

Normally, the secretion of thyroid hormone is controlled by a complex feedback mechanism involving the interaction of stimulatory and inhibitory factors (see the image below). Thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates the pituitary to release TSH.
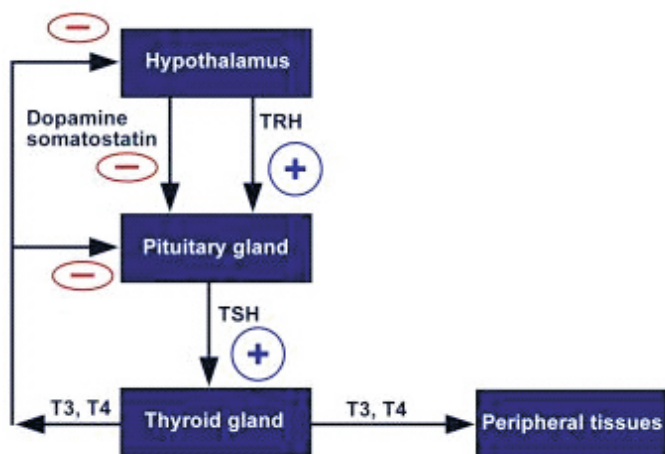
Hypothalamic-pituitary-thyroid axis feedback. Schematic representation of negative feedback system that regulates thyroid hormone levels. TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

Binding of TSH to receptors on the thyroid gland leads to the release of thyroid hormones—primarily T_4 and to a lesser extent T_3. In turn, elevated levels of these hormones act on the hypothalamus to decrease TRH secretion and thus the synthesis of TSH. Synthesis of thyroid hormone requires iodine. Dietary inorganic iodide is transported into the gland by an iodide transporter, converted to iodine, and bound to thyroglobulin by the enzyme thyroid peroxidase through a process called organification. This results in the formation of monoiodotyrosine (MIT) and diiodotyrosine (DIT), which are coupled to form T_3 and T_4; these are then stored with thyroglobulin in the thyroid's follicular lumen. The thyroid contains a large supply of its preformed hormones. Thyroid hormones diffuse into the peripheral circulation. More than 99.9% of T_4 and T_3 in the peripheral circulation is bound to plasma proteins and is inactive. Free T_3 is 20-100 times more biologically active than free T_4. Free T_3 acts by binding to nuclear receptors (DNA-binding proteins in cell nuclei), regulating the transcription of various cellular proteins. Any process that causes an increase in the peripheral circulation of unbound thyroid hormone can cause thyrotoxicosis. Disturbances of the normal homeostatic mechanism can occur at the level of the pituitary gland, the thyroid gland, or in the periphery. Regardless of etiology, the result is an increase in transcription in cellular proteins, causing an increase in the basal metabolic rate. In many ways, signs and symptoms of hyperthyroidism resemble a state of catecholamine excess, and adrenergic blockade can improve these symptoms. In Graves disease, circulating autoantibodies against the thyrotropin receptor provide continuous stimulation of the thyroid gland. These antibodies cause release of thyroid hormones and thyroglobulin, and they also stimulate iodine uptake, protein synthesis, and thyroid gland growth.

Ophthalmopathy

The underlying pathophysiology of Graves ophthalmopathy (also called thyroid-associated orbitopathy) is not completely characterized. It most likely involves an antibody reaction against the TSH receptor that results in activation of T cells against tissues in the retro-orbital space that share antigenic epitopes with thyroid follicular cells. These immune processes lead to an active phase of inflammation, with lymphocyte infiltration of the orbital tissue and release of cytokines that stimulate orbital fibroblasts to multiply and produce mucopolysaccharides (glycosaminoglycans), which absorb water. In consequence, the extraocular muscles thicken and the adipose and connective tissue of the retro-orbit increase in volume. Cigarette smoking and a high TSH receptor autoantibody level are significant risk factors for ophthalmopathy. In addition, patients who smoke appear to be more likely to experience worsening of their ophthalmopathy if treated with radioactive iodine, as do patients who have high pretreatment T_3 levels and post-therapy hypothyroidism.

Etiology

Genetic factors appear to influence the incidence of thyrotoxicosis. Autoimmune thyroid disease, including Hashimoto hypothyroidism and Graves disease, often occurs in multiple members of a family. Several genetic syndromes have been associated with hyperthyroidism, especially autoimmune thyroid disease. McCune-Albright syndrome is caused by mutations in the GNAS gene. This gene encodes the stimulatory G-protein alpha subunit, which is a key component of many signal transduction pathways. Patients present with the classic triad of polyostotic fibrous dysplasia, irregular café-au-lait spots, and precocious puberty. The syndrome may also include facial asymmetry, Cushing syndrome, hyperthyroidism, and acromegaly. A number of disorders of thyroid function have been found to be caused by mutations in the TSHR gene, which encodes the TSH receptor protein. These disorders include the following: Familial gestational hyperthyroidism. One type of nonimmune hyperthyroidism. Congenital nongoiterous

thyrotoxicosis. Toxic thyroid adenoma with somatic mutation. Type II autoimmune polyendocrine syndrome is associated with hyperthyroidism and hypothyroidism, as well as type 1 diabetes mellitus and adrenal insufficiency. Patients may also have immune deficiency, as manifested by chronic mucosal candidiasis.

Iodine intake

Iodine intake also appears to influence the occurrence of thyrotoxicosis. Clearly, patients in borderline iodine-deficient areas of the world develop nodular goiter, often with areas of thyroid autonomy. When members of this population move to areas of sufficient iodine intake, thyrotoxicosis occurs. Evidence exists that iodine can act as an immune stimulator, precipitating autoimmune thyroid disease and acting as a substrate for additional thyroid hormone synthesis.

Graves disease

The most common cause of thyrotoxicosis is Graves disease (50-60% of cases). Graves disease is an organ-specific autoimmune disorder characterized by a variety of circulating antibodies, including common autoimmune antibodies, as well as anti-TPO and anti-TG antibodies. The most important autoantibody is TSI, which is directed toward epitopes of the TSH receptor and acts as a TSH-receptor agonist. Like TSH, TSI binds to the TSH receptor on the thyroid follicular cells to activate thyroid hormone synthesis and release and thyroid gland growth (hypertrophy). This results in the characteristic picture of Graves thyrotoxicosis, with a diffusely enlarged thyroid, very high radioactive iodine uptake, and excessive thyroid hormone levels compared with a healthy thyroid.

A. Normal   B. Graves' disease

C. Toxic mng   D. Toxic adenoma
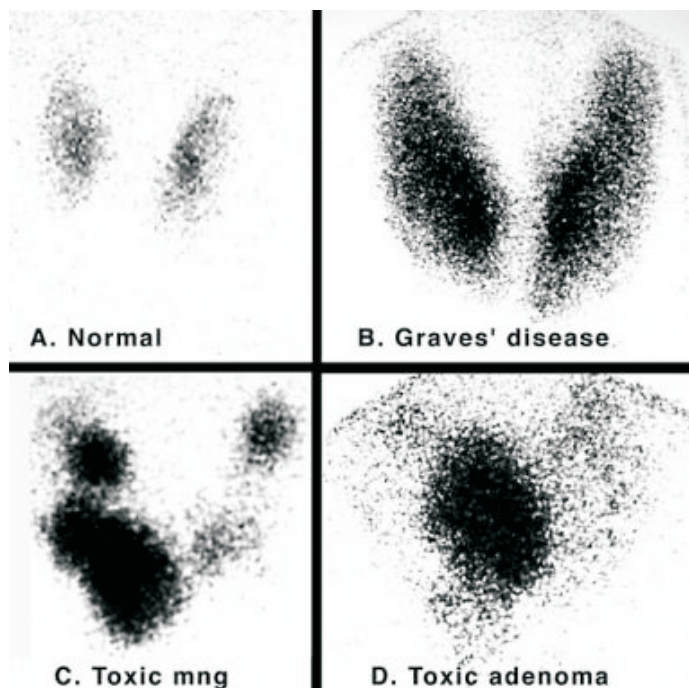
Iodine 123 (123I) nuclear scintigraphy: 123I scans of normal thyroid gland (A) and common hyperthyroid conditions with elevated radioiodine uptake, including Graves disease (B), toxic multinodular goiter (C), and toxic adenoma (D).

Thyroid hormone levels can be highly elevated in Graves disease. Clinical findings specific to Graves disease include thyroid ophthalmopathy (periorbital edema, chemosis [conjunctival edema], injection, or proptosis) and, rarely, dermopathy over the lower extremities. This autoimmune condition may be associated with other autoimmune diseases, such as pernicious anemia, myasthenia gravis, vitiligo, adrenal insufficiency, celiac disease, and type 1 diabetes mellitus.

Subacute thyroiditis

The next most common cause of thyrotoxicosis is subacute thyroiditis (approximately 15-20% of cases), a destructive release of preformed thyroid hormone. A typical nuclear scintigraphy scan shows no radioactive iodine uptake (RAIU) in the thyrotoxic phase of the disease. Thyroid hormone levels can be highly elevated in this condition.

Toxic multinodular goiter

Toxic multinodular goiter (Plummer disease) accounts for 15-20% of thyrotoxicosis cases. It occurs more commonly in elderly individuals, especially those with a long-standing goiter. Thyroid hormone excess develops very slowly over time and often is only mildly elevated at the time of diagnosis. Symptoms of thyrotoxicosis are mild, often because only a slight elevation of thyroid hormone levels is present, and the signs and symptoms of thyrotoxicosis often are blunted (apathetic hyperthyroidism) in older patients. However, very high thyroid hormone levels may occur in this condition after high iodine intake (eg, with iodinated radiocontrast or amiodarone exposure).

Toxic adenoma

Toxic adenoma is caused by a single hyperfunctioning follicular thyroid adenoma. This disorder accounts for approximately 3-5% of thyrotoxicosis cases. The excess secretion of thyroid hormone occurs from a benign monoclonal tumor that usually is larger than 2.5 cm in diameter. The excess thyroid hormone suppresses TSH levels. RAIU usually is normal, and the radioactive iodine scan shows only the hot nodule, with the remainder of the normal thyroid gland suppressed because the TSH level is low.

Other causes of thyrotoxicosis

Several rare causes of thyrotoxicosis exist that deserve mention. Struma ovarii is ectopic thyroid tissue associated with dermoid tumors or ovarian teratomas that can secrete excessive amounts of thyroid hormone and produce thyrotoxicosis. Iodide-induced thyrotoxicosis (Jod-Basedow syndrome) occurs in patients with excessive iodine intake (eg, from an iodinated radiocontrast study). The antiarrhythmic drug amiodarone, which is rich in iodine and bears some structural similarity to T_4, may cause thyrotoxicosis. Iodide-induced thyrotoxicosis also occurs in patients with areas of thyroid autonomy, such as a multinodular goiter or autonomous nodule. Iodide-induced thyrotoxicosis appears to result from loss of the normal adaptation of the thyroid to iodide excess. It is treated with cessation of the excess iodine intake and with administration of antithyroid medication. Usually, after depletion of the excess iodine, thyroid functions return to preexposure levels. Patients with a molar hydatidiform pregnancy or choriocarcinoma have extremely high levels of beta human chorionic gonadotropin (β-hCG), which can weakly activate the TSH receptor. At very high levels of β-hCG, activation of the TSH receptors is sufficient to cause thyrotoxicosis. Metastatic follicular thyroid carcinoma may also result in thyrotoxicosis. These lesions maintain the ability to make thyroid hormone, and in patients with bulky tumors, production may be high enough to cause thyrotoxicosis.

Epidemiology

Graves disease is the most common form of hyperthyroidism causing approximately 60-80% of cases of thyrotoxicosis. The annual incidence of Graves disease has been found to be 0.5 cases per 1000 population during a 20-year period, with the peak occurrence in people aged 20-40 years. Toxic multinodular goiter (15-20% of thyrotoxicosis) occurs more

frequently in regions of iodine deficiency. Toxic adenoma is the cause of 3-5% of cases of thyrotoxicosis.

Race-, sex-, and age-related demographics

Autoimmune thyroid disease occurs with the same frequency in Caucasians, Hispanics, and Asians but at lower rates in African Americans. All thyroid diseases occur more frequently in women than in men. Graves autoimmune disease has a male-to-female ratio of 1:5-10. The male-to-female ratio for toxic multinodular goiter and toxic adenoma is 1:2-4. Graves ophthalmopathy is more common in women than in men. Autoimmune thyroid diseases have a peak incidence in people aged 20-40 years. Toxic multinodular goiters occur in patients who usually have a long history of nontoxic goiter and who therefore typically present when they are older than age 50 years. Patients with toxic adenomas present at a younger age than do patients with toxic multinodular goiter.

Prognosis

Hyperthyroidism from toxic multinodular goiter and toxic adenoma is permanent and usually occurs in adults. After normalization of thyroid function with antithyroid medications, radioactive iodine ablation usually is recommended as the definitive therapy. Long-term, high-dose antithyroid medication is not recommended. Toxic multinodular goiters and toxic adenomas probably will continue to grow slowly in size during antithyroid pharmacotherapy. Generally, the thyrotoxic areas are ablated, and patients may remain euthyroid. Those who become hypothyroid after radioactive iodine therapy are easily maintained on thyroid hormone replacement therapy, with T_4 taken once daily. Patients with Graves disease may become hypothyroid in the natural course of their disease, regardless of whether treatment involves radioactive iodine or surgery. Eye disease may develop at a time distant from the initial diagnosis and therapy. Generally, after the diagnosis, the ophthalmopathy slowly improves over years. Thyroid hormone excess causes left ventricular thickening, which is associated with an increased risk of heart failure and cardiac-related death. Thyrotoxicosis has been associated with dilated cardiomyopathy, right heart failure with pulmonary hypertension, and diastolic dysfunction and atrial fibrillation. An increase in the rate of bone resorption occurs. Bone loss, measured by bone mineral densitometry, can be seen in severe hyperthyroidism at all ages and in both sexes. In mild subclinical disease, however, bone loss has been convincingly shown only in postmenopausal women.

History

The presentation of thyrotoxicosis is variable among patients. Thyrotoxicosis leads to an apparent increase in sympathetic nervous system symptoms. Younger patients tend to exhibit symptoms of sympathetic activation, such as anxiety, hyperactivity, and tremor, while older patients have more cardiovascular symptoms, including dyspnea and atrial fibrillation with unexplained weight loss. The clinical manifestations of thyrotoxicosis do not always correlate with the extent of the biochemical abnormality. Common symptoms of thyrotoxicosis include the following: ● Nervousness ● Anxiety ● Increased perspiration ● Heat intolerance ● Hyperactivity ● Palpitations. Generally, a constellation of information, including the extent and duration of symptoms, past medical history, and social and family history, in addition to the information derived from physical examination, help to guide the clinician to the appropriate diagnosis. For example, Graves disease is an autoimmune disease, and patients often have a family history or past medical history of autoimmune disease (eg, rheumatoid arthritis, vitiligo, pernicious anemia). Patients with Graves disease often

have more marked symptoms than patients with thyrotoxicosis from other causes, because thyroid hormone levels usually are the highest with this form of hyperthyroidism. The diagnosis of Graves disease should also be considered if any evidence of thyroid eye disease exists, including periorbital edema, diplopia, or proptosis. Toxic multinodular goiters occur in patients who have had a known nontoxic goiter for many years or decades. Often, patients have emigrated from regions of the world with borderline- low iodine intake or have a strong family history of nontoxic goiter. Subclinical hyperthyroidism, defined as a low thyroid-stimulating hormone (TSH) level with normal free thyroxine (FT_4) and free triiodothyronine (FT_3) levels, is associated with no or minimal clinical symptoms of thyrotoxicosis. However, certain conditions (eg, atrial fibrillation, osteoporosis, or hypercalcemia) may suggest the possibility of thyrotoxicosis. In fact, subclinical hyperthyroidism may be associated with a 3-fold increase in the risk of atrial fibrillation. The prevalence of subclinical hyperthyroidism may be as high as 2% in the general population. The risk of atrial fibrillation may be elevated even in persons with high-normal thyroid function. In a report from the Netherlands on 1426 patients whose TSH levels were in the normal range (0.4-4.0 mIU/L), the hazard ratio for atrial fibrillation was 1.94 for the lowest versus the highest quartile of TSH, after a median follow-up of 8 years. Radiation exposure increases the risk of benign and malignant nodular thyroid diseases, especially with the higher radiation levels used in radiation therapy. External radiation therapy is associated with an increase in the incidence of autoimmune hyperthyroidism when the thyroid is in the radiation field. The family history should include careful documentation of the following: ● Autoimmune disease ● Thyroid disease ● Emigration from iodine-deficient parts of the world. Review a complete list of medications and dietary supplements. A number of compounds—including expectorants, amiodarone, iodinated contrast dyes, and health food supplements containing seaweed or thyroid gland extracts—contain large amounts of iodine that can induce thyrotoxicosis in a patient with thyroid autonomy. Rarely, iodine exposure can cause thyrotoxicosis in a patient with an apparently healthy thyroid.

Physical Examination

The thyroid is located in the lower anterior neck. The isthmus of the butterfly-shaped gland generally is located just below the cricoid cartilage of the trachea, with the wings of the gland wrapping around the trachea. Physical examination often can help the clinician to determine the etiology of thyrotoxicosis. Common signs of thyrotoxicosis include the following: ● Tachycardia or atrial arrhythmia ● Systolic hypertension with wide pulse pressure ● Warm, moist, smooth skin ● Lid lag ● Stare ● Hand tremor ● Muscle weakness ● Weight loss despite increased appetite (although a few patients may gain weight, if excessive intake outstrips weight loss) ● Reduction in menstrual flow or oligomenorrhea.

Thyroid examination

Thyrotoxicosis from Graves disease is associated with a diffusely enlarged and slightly firm thyroid gland. Sometimes, a thyroid bruit can be heard by using the bell of the stethoscope. Toxic multinodular goiters generally occur when the thyroid gland is enlarged to at least 2 to 3 times the normal size. The gland often is soft, but individual nodules occasionally can be palpated. Because most thyroid nodules cannot be palpated, thyroid nodules should be documented by thyroid ultrasonography, but overactive thyroid nodules can be demonstrated only by nuclear thyroid imaging with radioiodine (I-123) or technetium (Tc99m) thyroid scan. If the thyroid is enlarged and painful, subacute painful or granulomatous thyroiditis is the likely diagnosis. However,

degeneration or hemorrhage into a nodule and suppurative thyroiditis should also be considered.

Ophthalmologic and dermatologic examination

Approximately 50% of patients with Graves thyrotoxicosis have mild thyroid ophthalmopathy. Often, this is manifested only by periorbital edema, but it also can include conjunctival edema (chemosis), injection, poor lid closure, extraocular muscle dysfunction (diplopia), and Proptosis ow). Evidence of thyroid eye disease and high thyroid hormone levels confirms the diagnosis of autoimmune Grave disease.

Severe proptosis, periorbital edema, and eyelid retraction from thyroid-related orbitopathy. This patient also had optic nerve dysfunction and chemosis (conjunctival edema) from thyroid-related orbitopathy.

In rare instances, Graves disease affects the skin through deposition of glycosaminoglycans in the dermis of the lower leg. This causes nonpitting edema, which is usually associated with erythema and thickening of the skin, without pain or pruritus (see the image below).
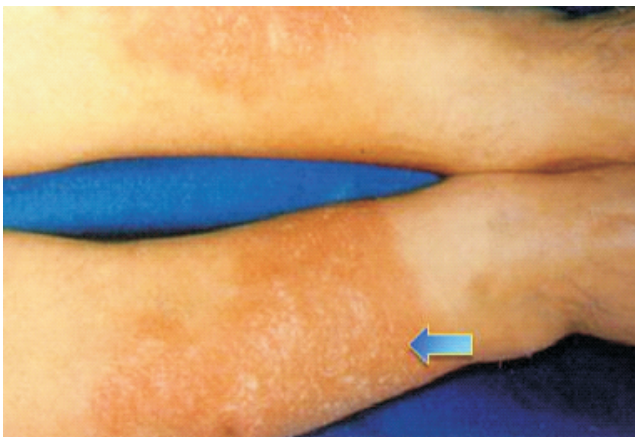
Bilateral erythematous infiltrative plaques on lower extremities in 42-year-old man with Graves disease are consistent with pretibial myxedema. Myxedematous changes of skin usually occur in pretibial areas and resemble orange peel in color and texture.

Diagnostic Considerations

Diagnostic considerations include factitious hyperthyroidism, which is hyperthyroidism secondary to intentional consumption of thyroid hormone. In this condition, thyroid hormone consumption causes suppression of thyroglobulin secretion by the thyroid. Factitious hyperthyroidism is common in medical personnel, who have easy access to medication containing thyroid hormone and may abuse it for weight loss or an energy boost.

Differential Diagnoses
- Diffuse Toxic Goiter (Graves Disease)
- Euthyroid Hyperthyroxinemia
- Goiter
- Graves Disease
- Struma Ovarii
- Thyrotoxicosis Imaging

Approach Considerations

The most reliable screening measure of thyroid function is the thyroid-stimulating hormone (TSH) level. TSH levels usually are suppressed to unmeasurable levels (< 0.05 µIU/mL) in thyrotoxicosis. The degree of thyrotoxicosis is determined by measurement of thyroid hormone levels; the severity of clinical manifestations often does not correlate with the degree of thyroid hormone elevation. The most specific autoantibody test for autoimmune thyroiditis is an enzyme-linked immunosorbent assay (ELISA) test for anti-thyroid peroxidase (anti-TPO) antibody. The titers usually are significantly elevated in the most common type of hyperthyroidism, Graves thyrotoxicosis, and usually are low or absent in toxic multinodular goiter and toxic adenoma. If the etiology of thyrotoxicosis is not clear after physical examination and other laboratory tests, it can be confirmed by means of scintigraphy. The degree and pattern of isotope uptake indicate the type of thyroid disorder. Older patients with hyperthyroidism often present with atrial arrhythmias or heart failure. Electrocardiography is recommended if an irregular or elevated (> 100 beats/min) heart rate or signs of heart failure are noted upon examination.

TSH and Thyroid Hormone Levels

Although measurement of the TSH level is the most reliable screening method for assessing thyroid function, the degree of thyrotoxicosis cannot be estimated easily in this way. Instead, thyrotoxicosis must be measured using an assay of thyroid hormone levels in the plasma. Thyroid hormone circulates as triiodothyronine (T_3) and thyroxine (T_4), with more than 99.9% of the hormones bound to serum proteins (especially thyroxine-binding globulin, transthyretin or thyroxine-binding prealbumin, and albumin). Measuring free T_4 (FT_4) and total T_3 is recommended in patients with suspected thyrotoxicosis when TSH is low. Patients with milder thyrotoxicosis may have elevation of T_3 levels only. Many laboratories do not measure FT_4 directly, instead using a calculation to estimate the FT_4 level. The free thyroxine index (FTI) is equal to total T_4 multiplied by the correction for thyroid hormone binding, such as the thyroid hormone binding ratio (THBR) or T_3 resin uptake [T_3 RU]). A similar calculation can be used with total T_3. Thyrotoxicosis is marked by TSH levels suppressed below the reference range (usually 0.4-4 mIU/L) and elevated thyroid hormone levels. Subclinical hyperthyroidism is defined as a decreased but not undetectable TSH level (< 0.5 µIU/mL in many laboratories) in combination with serum concentrations of T_3 and T_4 that are within the reference range. Because nonthyroidal illness will produce temporary suppression of TSH, thyroid function tests should be repeated before therapy is instituted for subclinical disease. Hormonal changes in pregnancy can complicate the interpretation of thyroid function tests. Physiologic maximum elevation of beta human chorionic gonadotropin (β-hCG) at the end of the first trimester of pregnancy is associated with a mirror-image temporary reduction in TSH. Despite the reduction in TSH, FT_4 levels usually remain normal or only slightly above the reference range. As the pregnancy progresses and β-hCG plateaus at a lower level, TSH levels return to normal.

Autoantibody Studies

The most specific autoantibody test for autoimmune thyroiditis is an ELISA test for anti-TPO antibody. The titers usually are significantly elevated in the most common type of hyperthyroidism, Graves thyrotoxicosis, and usually are low or absent in toxic multinodular goiter and toxic adenoma. A significant number of healthy people without active thyroid disease have mildly positive anti-TPO antibody titers; thus, the test should not be performed for screening purposes. The thyroid-stimulating immunoglobulin (TSI) level, if elevated, helps to establish the diagnosis of Graves disease. Circulating antithyroglobulin (anti-TG) antibodies are also present in Graves disease; however, testing for these antibodies should not be used, because anti-TG antibodies by themselves may be present in persons without other evidence of thyroid dysfunction.

Scintigraphy

If the etiology of thyrotoxicosis is not clear after physical examination and other laboratory tests, it can be confirmed by means of scintigraphy. Iodine-123 (^{123}I) or technetium-99m (^{99m}Tc) can be used for thyroid scanning. Normally, the isotope distributes homogeneously throughout both lobes of the thyroid gland. In patients with hyperthyroidism, the pattern of uptake (eg, diffuse vs nodular) varies with the underlying disorder. The overall level of radioactive iodine uptake (RAIU) also varies with different conditions. Normal RAIU is approximately 5-20% but is modified by the iodine content of the patient's diet.

Thyrotoxicosis and Hyperthyroidism

Common Forms (85-90% of Cases)	24-Hour RAIU Over Neck*
Diffuse toxic goiter (Graves disease)	Increased (moderate to high: 40-100%)
Toxic multinodular goiter (Plummer disease)	Increased (mild to moderate: 25-60%)
Thyrotoxic phase of subacute thyroiditis	Decreased (very low: < 2%)
Toxic adenoma	Increased (mild to moderate: 25-60%)
Less Common Forms	
Iodide-induced thyrotoxicosis	Variable but usually low (< 25%)
Thyrotoxicosis factitia	Decreased (very low: < 2%)
Uncommon Forms	
Pituitary tumors producing TSH	Increased (mild to moderate: 25-60%)
Excess human chorionic gonadotropin (molar pregnancy/choriocarcinoma)	Increased (variable: 25-100%)
Pituitary resistance to thyroid hormone	Increased (mild to moderate: 25-60%)
Metastatic thyroid carcinoma	Decreased
Struma ovarii with thyrotoxicosis	Decreased

RAIU = radioactive iodine uptake; TSH = thyroid-stimulating hormone.
* A normal 6-hour RAIU is approximately 2-16%; a 24-hour RAIU is about 8-25% but is modified according to the iodine content of the patient's diet. RAIU or scanning should not be performed in a woman who is pregnant (with the exception of a molar pregnancy) or breastfeeding.

Approach Considerations

Treatment of hyperthyroidism includes symptom relief, as well as antithyroid pharmacotherapy, radioactive iodine-131 (^{131}I) therapy (the preferred treatment of hyperthyroidism among US thyroid specialists), or thyroidectomy. However, antithyroid medications are not effective in thyrotoxicosis in which scintigraphy shows low uptake of iodine-123 (^{123}I), as in patients with subacute thyroiditis, because these cases result from release of preformed thyroid hormone. If a physician treats enough patients who are hyperthyroid, eventually he or she will encounter a patient who develops agranulocytosis or hepatitis from the antithyroid medications. Discussing these adverse effects with patients before starting therapy is important; accordingly, patients should be given written or documented verbal instruction to the effect that if they develop high fever (>100.5°F) or a severe sore throat, they should stop the medication and seek medical attention.

Management of Ophthalmopathy

Although 50% of patients with Graves disease have mild signs and symptoms of thyroid eye disease, only 5% develop severe ophthalmopathy (eg, diplopia, visual-field deficits, or blurred vision). Less serious ophthalmologic symptoms (eg, photophobia, irritation, and tearing) are treated with tight-fitting sunglasses, which should be worn at all times when the patient is outside, and with saline eye drops that are taken as necessary for comfort. If exposure keratitis is suspected, the patient should be monitored by an ophthalmologist. This condition usually occurs when eyelid closure is incomplete and the cornea is exposed at night, when the patient does not blink. Typically, patients complain of irritation and tearing on awakening. Treatment includes administering saline gel or drops and taping eyelids closed with paper tape before sleep. Some ophthalmologists are concerned about corneal abrasion from the tape and instead recommend that patients wear goggles at night to keep the eyes moist. A medical emergency occurs when sufficient orbital edema exists to cause optic nerve compression with early loss of color vision and orbital pain. Without treatment, continued pressure on the optical nerve may cause permanent vision loss. High-dose glucocorticoids are administered, with consideration for orbital decompression surgery and ocular radiation therapy.

Management of Dermopathy

Infiltrative dermopathy, usually developing over the lower extremities, is characterized by an accumulation of glycosaminoglycans and inflammatory cells in the dermis. The skin changes typically include a nonpitting erythematous edema of the anterior shins. Dermopathy can occur at other sites of repeat trauma. The dermopathy usually occurs only in the presence of significant ophthalmopathy. No effective treatment exists. Nightly occlusive wraps of the affected site are recommended, with plastic wrap used after the application of a high-potency topical steroid cream.

Relief of Symptoms

Many of the neurologic and cardiovascular symptoms of thyrotoxicosis are relieved by beta-blocker therapy. Before such therapy is initiated, the patient should be examined for signs and symptoms of dehydration that often occur with hyperthyroidism. After oral rehydration, beta-blocker therapy can be started. Beta-blocker therapy should not be administered to patients with a significant history of asthma. Calcium channel blockers (eg, verapamil and diltiazem) can be used for the same purposes when beta-blockers are contraindicated or poorly tolerated. These therapies should be tapered and stopped once thyroid functions are within the normal range.

Management

Treatment of hyperthyroidism includes symptom relief, as well as therapy with antithyroid medications, radioactive iodine-131 (^{131}I), or thyroidectomy. Symptomatic treatment is as follows: ● Oral rehydration for dehydrated patients ● Beta-blockers for relief of neurologic and cardiovascular symptoms ● For mild ophthalmopathy, saline eye drops as needed and tight-fitting sunglasses for outdoors ● For vision-

threatening ophthalmopathy, high-dose glucocorticoids, with consideration for orbital decompression surgery and ocular radiation therapy. Antithyroid drug treatment is as follows: ● Used for long-term control of hyperthyroidism in children, adolescents, and pregnant women ● In adult men and nonpregnant women, used to control hyperthyroidism before definitive therapy with radioactive iodine ● Methimazole is more potent and longer-acting than propylthiouracil ● Propylthiouracil is reserved for use in thyroid storm, first trimester of pregnancy, and methimazole allergy or intolerance ● Antithyroid drug doses are titrated every 4 weeks until thyroid functions normalize ● Patients with Graves disease may experience remission after treatment for 12-18 months, but recurrences are common within the following year ● Toxic multinodular goiter and toxic adenoma will not go into remission. Radioactive iodine treatment is as follows: ● Preferred therapy for hyperthyroidism ● Administered orally as a single dose in capsule or liquid form ● Causes fibrosis and destruction of the thyroid over weeks to many months ● Hypothyroidism is expected ● Pregnancy, breast feeding, and recent lactation are contraindications ● Radioactive iodine should be avoided in children younger than 5 years ● Radioactive iodine is usually not given to patients with severe ophthalmopathy. Thyroidectomy is reserved for special circumstances, including the following: ● Severe hyperthyroidism in children ● Pregnant women who are noncompliant with or intolerant of antithyroid medication ● Patients with very large goiters or severe ophthalmopathy ● Patients who refuse radioactive iodine therapy ● Refractory amiodarone-induced hyperthyroidism ● Patients who require normalization of thyroid functions quickly, such as pregnant women, women who desire pregnancy in the next 6 months, or patients with unstable cardiac conditions. Guidelines for the management of hyperthyroidism and other causes of thyrotoxicosis have been developed by the American Thyroid Association and the American Association of Clinical Endocrinologists. These guidelines include 100 evidence-based recommendations concerning the care of these patients.

Diet and Activity

No special diet must be followed by patients with thyroid disease. However, some expectorants, radiographic contrast dyes, seaweed tablets, and health food supplements contain excess amounts of iodide and should be avoided because the iodide interferes with or complicates the management of antithyroid and radioactive iodine therapies. Exercise tolerance often is not significantly affected in otherwise healthy patients with mild to moderate hyperthyroidism. For these patients, no reduction in physical activity is necessary. For patients who are elderly or have cardiopulmonary comorbidities or severe hyperthyroidism, a decrease in activity is prudent until hyperthyroidism is medically controlled. With severe thyrotoxicosis, systolic and diastolic cardiac dysfunction often result in dyspnea on exertion. Beta-blocker therapy often greatly improves exercise tolerance until thyroid hormones levels are reduced by other therapies.

INTERPRETATION

Thyroid Levels in Different Disease Conditions

Disease	T3	T4	TSH	FT3	FT4	T-Uptake	Tg	Anti-TPO	TRH	TBG
Primary Hypothyroidism	↓	↓	↑	↓	↓	↓			R	
Hyperthyroidism	↑	↑	↓	↑	↑	↑	↑			
Pituitary insuffiency, tertiary hypothroidism		↓	↓		↓	↓			R*	
T3, thyrotoxicosis				↑	↓				R	
Subacute thyroiditis		↑	↓		↑	↑a , ↓b	↑			
Nontoxic nodular goiter					↑		↑			
Graves disease				↑	↑			↑		
Hashimoto thyroiditis				↑		↑d, ↓e		↑		
Lymphadenoid goiter								↑		
Iatrogenic hyperthyroidoidism					↑					
Myxedema			↑		↓					
Estrogen therapy, oral contraceptives, pregnancy		↑	↓c			↓				↑
Androgen therapy, steroid, hypoproteinemia (nephrosis, cirrhosis)		↓				↑				
Hypothyroidism treated with thyroxine					↓					
Hypothyroidism treated with Triiodothyronine					↑					
Anti-thyroid drug for thyrotoxicosis		↓, N	↓			↓				
Benign adenoma							↑			
Untreated and metastatic carcinoma of thyroid							↑			
Acute psychiatric illness, acute medical illness, hepatic disease, malnutrition, addisons disease, acromegaly					↓					

a–recovery stage, b- active stage, c- 1st trimester, d- early, e-late, R- respose, R*- delayed response, ↓-decrease, ↑ increase

BOUQUET

In Lighter Vein

A man asks a farmer near a field, "Sorry sir, would you mind if I crossed your field instead of going around it You see, I have to catch the 4:23 train." The farmer says, "Sure, go right ahead. And if my bull sees you, you'll even catch the 4:11 one."

At a swimming pool: Three guys climb a high-dive tower and meet a good fairy who offers to fulfill a wish for each of them. One jumps and says, "Beer!" - and the pool is full of beer. The other one jumps, says, "Money!" and the pool is full of money. The last one starts to jump but slips and, falling, yells, "SHIIIIIIT!!!"

An elderly man was on the operating table, about to be operated on by his son, a famous surgeon. Just before they put him under, he asked to speak to his son: "Don't be nervous, boy, just do your best and just remember, if it doesn't go well, if something happens to me… your mother is going to come and live with you and your family."

An eskimo brings his friend to his home for a visit. When they arrive, his friend asks, puzzled – "So where's your igloo "
"Oh no, I must've left the iron on…"

An old guy in his Volvo is driving home from work when his wife rings him on his cell phone.
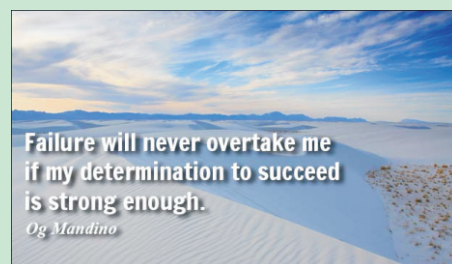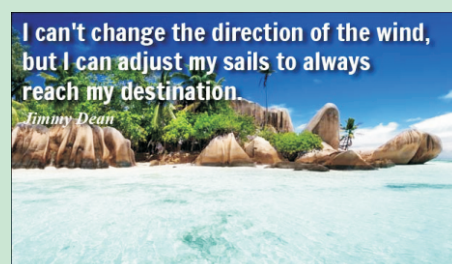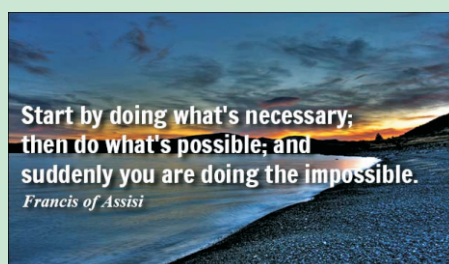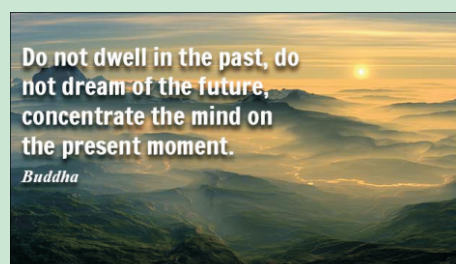"Honey," she says in a worried voice, "please be careful. There was a bit on the news just now, some lunatic is driving the wrong way down the highway."
"Oh it's worse than that," he replies, "there are hundreds of them!"

Brain Teasers

1. Which of the following antibodies is present on the surfaces **of B cells?**
   A. IgG
   B. IgD
   C. IgM
   D. IgE.

2. **Which of the following antibodies is pentameric in structure?**
   A. IgG
   B. IgD
   C. IgM
   D. IgE.

3. **What kind of a test is VDRL?**
   A. Complement assay
   B. Agglutination
   C. Flocculation
   D. Immunodiffusion.

4. **What kind of a test is blood grouping ?**
   A. Complement assay
   B. Agglutination
   C. Flocculation
   D. Immunodiffusion.

5. **What kind of test is pregnancy card/strip test?**
   A. Complement assay
   B. Agglutination
   C. Flocculation
   D. Immunochromatography.

Wisdom Whispers

Do not dwell in the past, do not dream of the future, concentrate the mind on the present moment.
Buddha

Start by doing what's necessary; then do what's possible; and suddenly you are doing the impossible.
Francis of Assisi

I can't change the direction of the wind, but I can adjust my sails to always reach my destination.
Jimmy Dean

Life is really simple, but we insist on making it complicated.
Confucius

The best preparation for tomorrow is doing your best today.
H. Jackson Brown, Jr.

Failure will never overtake me if my determination to succeed is strong enough.
Og Mandino

TROUBLESHOOTING

Problems in the Interpretation of Thyroid Function Tests

It is difficult to guarantee reliable thyroid function results in patients with nonthyroidal llness. Abnormal results may occur in patients with infections, malignancy, myocardial infarction, following surgery, etc., who do not have thyroid disease. Typically, during the acute phase of an illness, free T3 (FT3) concentration and less often, free T4 (FT4) concentration is decreased. The TSH is usually normal but may be undetectable in the severely ill. During recovery, TSH may rise transiently into the hypothyroid range as free hormone concentrations return to normal. In chronic illness, for example, chronic renal failure, free hormone concentrations are decreased (to an extent that may reflect the severity of the underlying disease); TSH is usually normal, but it is occasionally decreased. The occurrence of abnormalities of thyroid function tests in patients with nonthyroidal illness has been termed the 'Sick Euthyroid Syndrome'. Causes include decreased peripheral conversion of T4 to T3; changes in the concentration of binding; increased plasma concentrations of free fatty acids, which displace thyroid hormones from their binding sites, and nonthyroidal influences on the hypothalamicpituitary- thyroid axis, for example, by cortisol, which can inhibit TSH secretion. Furthermore, many drugs can influence the results of tests of thyroid function. Many times, the levels of FT3, FT4 and TSH do not correlate.

Common Causes of TSH/FT4/FT3 Discrepancies
● Over replacement of thyroid hormone (TSH low, free T4 normal) ● Recent dose adjustment (TSH high, free T4 normal) ● Patient taking T3 (TSH low, free T4 normal) ● Patient noncompliant with hormone replacement (TSH high, free T4 normal) ● Nonthyroidal illness ● Drugs affecting thyroid hormones: Glucocorticoids, dopamine ● Thyroid hormone resistance (TSH high, freeT4 high, patient euthyroid) ● TSH-secreting tumour (TSH high, free T4high, patient hyperthyroid) ● During antithyroid drug therapy, there can be patients who have persistent serum T3 excess, despite normal or low serum T4 values.

Effects of Drugs on Thyroid Function
● Altered hypothalamic or pituitary function ● Altered biosynthesis or release of thyroid hormones ● Displacement of T4 and T3 from binding proteins ● Reduced peripheral conversions of T4 to T3 ● Inhibition of peripheral hormone activity.

Drugs that Affect Results of Thyroid Function Tests

Drugs	Effect	Cause
Salicylates, Phenylbutzone, Dphenylhydantoin	Total T4 and T3 reduced, Free T4 normal	Inhibition of serum protein binding
Propylthiouracil, Methimazole, release Lithium, Iodides	Total T4 and T3 reduced	Inhibition of TSH production or
Propylthiouracil	Total T3 reduced both T4 and	Inhibition of conversion of T4 to T3

Propranolol	Total T3 reduced, T4 normal, TSH normal	Inhibition of conversion of T4 to T3
Glucocorticoids	Total T3 reduced, T4 and TSH low or normal	Inhibition of conversion of T4 to T3
Oral radiographic dyes	Total T3 reduced, both T4 and TSH high	Inhibition of conversion of T4 to T3
Dopamine, L-dopa, Glucocorticoids	Basal TSH and response to TRH reduced	Direct effect to inhibit TSH Production in pituitary gland
Amiodarone, Bensamide (transient), Metopramide, Sulpiride	Basal TSH increased TRH,	Increased TSH production

Relationship Between Serum Total T4 and Total T3 Concentrations in Various Disorders

		Serum T4 Concentration		
		LOW	NORMAL	HIGH
Serum T3 Concentration	High	Iodide deficiency, T3 treatment, Antithyroid drug therapy,	T3 – thyrotoxicosis, T3 – binding auto-antibodies,	Thyrotoxicosis of any cause, Excess T4 ingestion Thyroid hormone resistance, TBG excess,
	Normal	Iodine deficiency, T3 treatment, Hypothy-roidism		T4 treatment, Euthyroid hyperthy-roxinemia, Thyrotoxicosis with acute or moderate nonthyroidal illness, T4 binding autoantibodies
	Low	Severe hypothy-roidism, TBG deficiency, Drugs, Severe nonthyroidal illness,	Acute and chronic non-thyroidal illness, Drugs, Fetal life, Restricted nutrition	Thyrotoxicosis with severe nonthyroidal illness,

Relationship Between Serum FT4, FT3 and TSH Concentrations in Various Disorders

		Serum T4 Concentration		
		HIGH	NORMAL	LOW
Serum TSH Concentration	High	TSH-secreting tumor (rare) (FT3 = ↑)	Borderline/compensated hypothyroidism,	Hypothyroid (primary), Recovery from sick euthyroid state,
	Normal	Euthyroid with T4 autoantibodies (uncommon)	Euthyroid	Sick euthyroid (FT3 = ↓), Hypopituitarism (other pituitary hormones = ↓),
	Low	Hyperthyroidism (FT3 = ↑)	T3 thyrotoxicosis (FT3 = ↑), Sub-clinical hyperthyroidism (FT3 = N/↓),	Hypopituitarism (other pituitary hormones = ↓), Sick euthyroid (severe) (FT3 = ↓),

Free Thyroxine Measurements in Common Conditions Affecting Thyroid-Binding Proteins

Clinical conditions	Free T4 Levels
Near Normal Concentration of Serum-Binding Proteins	
Hypothyroidism	Low
Hyperthyroidism	High
Hyperoestrogenism	Low
Abnormal Concentration of Serum-Binding Proteins	
TBG excess	Normal
TBG deficiency	High
Dysalbuminaemia	Normal
Hypoalbuminaemia	Normal
T4 autoantibody	Normal
Low total T4 non-thyroidal illness	Normal or High
High total T4 Non-thyroidal illness	Normal or High

Free T4 and Free T3 in Various Disease Conditions

1. Hyperthyroidism

Hyperthyroidism produces a primary increase in Free T4, whereas oestrogens and idiopathic or genetic conditions may produce a primary increase in TBP. In both cases [T4 and TBP] increase, but in the former, the patient is ill and requires treatment; in the latter, the patient is euthyroid. Likewise, a low serum [T4 and TBP] may be due to a primary decrease in [FT4] or to a primary decrease in [TBP]. It is, therefore, clinically important to differentiate between changes in [T4 and TBP] that are due to primary changes in [FT4] (e.g. hyper-or hypothyroidism) and those that are due to primary changes in [TBP]. Serum TSH level is low in all forms of hyperthyroidism except in rare cases in which hyperthyroidism is mediated by TSH itself. When TSH level is low, free T4 concentration should be measured and will be elevated in most cases of hyperthyroidism. Finding a low TSH level and an elevated free T4 level is usually sufficient to establish the diagnosis of hyperthyroidism. If TSH level is low but free T4 level is normal, a T3 measurement should be performed, since serum T3 concentration is often elevated earlier in the course of hyperthyroidism and to a greater degree than is T4 concentration. Because only the free fraction of T3 is active, the estimation of free T3 is helpful in adjusting the total T3 for variations in binding proteins. It should be remembered that numerous medications as well as both acute and chronic illness may cause a transient lowering of T3 concentration as well as a reduction in TSH level. In Grave's disease or toxic adenomas, serum total T3 and free T3 levels are typically elevated to a greater degree than total T4 and free T4. T3 toxicosis—encountered in about 5 per cent of hyperthyroid population—total T3 and free T3 values increase. Serum total T4 and free T4 are disproportionately elevated to a greater degree than total T3 and Free T3 values in most patients with toxic multinodular goitre. Monitoring total T3 and free T3 values may also be of importance in evaluating both the severity and the response therapy in patients being treated for thyroid storm or crisis in that the antithyroid drug therapies are focused on reducing both thyroid gland T3 secretion and peripheral tissue T3 production from T4.

2. Nonthyroidal Illness

In nonthyroidal illness (NTI) and altered states of nutrition there are two categories: *Low T3 state:* Decrease in total T3 and free T3while maintaining normal total T4 and free T4. Observed in mild or moderate NTIs or states of caloric deprivation (< 400 cal) *Low T3-T4 state:* Total T4 also decreased, a case of severe NTI. Free T4 levels remain within or near the normal range of values as serum total T4levels decline. Decreased total T3 or normal free T4 or increased free T4 results from acquired defect in serum T4-binding proteins which accompany NTI. Also common are increases in the levels of the free fraction of T4 and T3 which are caused by decrease in serum concentrations of thyroid hormone-binding proteins, changes in binding properties induced by circulating inhibitors and drugs, or both. Low levels of total T4 may be seen in nonthyroidal illnesses, but total T4 concentrations in these patients are usually normal or above normal as determined using reference methods. Thus in nonthyroidal illnesses, abnormal thyroid test results are not necessarily indicative of thyroid disease but may demonstrate adaptations to the catabolic state, many of these changes revert to normal when the patient recovers. Several test abnormalities may be seen in nonthyroidal illnesses in euthyroid patients (the 'euthyroid sick syndrome'). The most common abnormalities are a reduction in the serum total T3 concentration and an elevation in the serum level of fT3. Also common are increases in the levels of the free fraction of T4 and T3 which are caused by decrease in serum

concentrations of thyroid hormonebinding proteins, changes in binding properties induced by circulating inhibitors and drugs, or both. Low levels of total T4 may be seen in nonthyroidal illnesses, but total T4 concentrations in these patients are usually normal or above normal as determined using reference methods.

3. Hypothyroidism

If total T4 (or free T4) level is normal, hypothyroidism is most unlikely: however, a low T4 concentration is often seen in the euthyroid sick.

Assay Choice Application

For definitive diagnosis, assessment of both serum TSH and free T4 is required, but a more limited approach can be used for initial case finding and follow-up. In the interests of cost effectiveness, evaluation of thyroid status may often begin with an assay for either serum TSH or free T4, followed by further algorithm-based assessment if the initial result is abnormal. As an initial test, serum total T4 measurements givean unacceptable rate of abnormal results, due to the frequency of abnormalities in serum thyroid hormone-binding proteins. Four distinct clinical situations in which evaluation of thyroid function is done can be considered: testing of unselected populations for case finding or screening, testing of untreated patients who have clinical features that suggest thyroid disease, assessment of the response to treatment for thyroid dysfunction, and evaluation of patients in whom associated illness or drug therapy are likely to complicate clinical and laboratory assessment or whose initial results are atypical or unclear.

Screening and Case Finding

About 2 per cent to 7 per cent of women over age 40 years may have slightly elevated serum TSH concentrations. The case for routine assessment of thyroid status is strongest in elderly women who have any symptoms that could be consistent with hypothyroidism. Among hospitalised patients, the large majority of abnormal results are due to nonthyroidal illness or medications. Most persons found to have either high or low serum TSH values in screening or casefinding studies have subclinical disease. That is, they have no clinical manifestations of thyroid dysfunction and normal serum free T4 and T3 concentrations. Regardless of which initial test is used, assessment of thyoid status has a high priority in patients at increased risk of having thyroid dysfunction, as for example in those with goitre, those treated previously for thyrotoxicosis or receiving lithium or amiodarone, and patients with associated autoimmune disease or connective tissue diseases or a history of neck or whole body irradiation.

Untreated Patients

In untreated ambulatory patients, a normal serum TSH concentration has high negative predictive value in ruling out thyroid disease. If serum TSH is abnormal, serum free T4 is done. Diagnostic strategies have been evaluated in which serum T4 measurements are done routinely only if the serum TSH is abnormal, unless pituitary disease is suspected. Long-term assessment of this approach will need to balance cost savings against potentially serious adverse outcomes; for example, if thyrotoxicosis is missed because of normal serum TSH values, or central hypothyroidism is missed on the basis of normal serum TSH values. The following groups of patients will be incompletely or incorrectly assessed if either serum TSH or free TSH or free T4 alone is measured. Patients with subclinical hypothyroidism (high serum TSH, normal free T4) in whom replacement therapy may be beneficial. Those with subclinical thyrotoxicosis (low serum TSH, normal free T4) in whom treatment with an antithyroid drug or thyroid ablation may be beneficial. Those being treated for thyrotoxicosis, in whom suppression of TSH secretion may persist for weeks or months after normalization of serum T4 and T3 on drug. Those with central (secondary or hypothyrotropic) hypothyroidism

(low serum free T4 low or normal TSH), who should be evaluated for adrenal insufficiency before T4 therapy is initiated. Those with binding abnormalities such as familial dysalbuminaemic hyperthyroxinaemia (FDH) or T4 or T4 binding autoantibodies in whom some serum free T4 estimates are invalid. Those with thyroid hormone resistance with high serum T4 and T3 concentrations and normal or high serum TSH concentrations, who are often not recognised until after inappropriate treatment has been given. Those with thyrotoxicosis caused by excess TSH secretion caused by a pituitary tumour or selective pituitary resistance to thyroid hormone. Not withstanding the widespread acceptance of serum TSH as a single initial test, some still advocate an estimate of free T4 as the best initial test for suspected thyrotoxicosis.

Assessment of the Response to Treatment

In the testing of ambulatory patients with known thyroid disease, the use of serum TSH alone can also be considered. In a study of ambulatory patients attending a thyroid clinic, hyperthyroid patients taking T4 for either replacement or suppression, seldom needed a serum free T4 measurement of the serum TSH was greater than 0.05 mU/L; although at lower values, the magnitude of hyperthyroxinaemia did influence management. In contrast, in patients with newly diagnosed thyrotoxicosis, measurements of serum free T4 or free T3, or both, were necessary in addition to serum TSH not only to establish the degree of hormone excess but also to evaluate the response to treatment. This study included a few new cases of hypothyroidism, in whom serum T4 measurement also would be required to establish the degree of hormone deficiency. In patients with thyroiditis and pituitary-hypothalamic disease, combined assessment was required. In evaluating patients receiving T4 therapy, some have suggested that hormone measurements add little to a clinical assessment made by experts, but there is justification for periodic serum TSH assessment to avoid subtle tissue effects of thyroid hormone excess of deficiency. A serum TSH value in the low-normal range is, probably, the best single indicator of appropriate dosage and is certainly of more use than a serum free T4 value alone, which may be increased slightly depending on the time interval between dose and sampling. In some situations (e.g. patients with ischaemic heart disease and hypothyroidism), the appropriate dose of T4 should be based on clinical judgement rather than laboratory findings.

Difficult Diagnostic Situations

The prevalence of abnormal serum T4 or TSH values in patients with acute medical or psychiatric illness is high, but there is controversy as to the value of thyroid function testing in these situations, because most of the abnormalities do not indicate the presence of thyroid disease in acutely ill patients because of the potential importance of intercurrent thyroid disease and the difficulty in assessing clinical features of thyroid dysfunction, others suggest that testing should not be done without some clinical indication. In patients hospitalised for acute illness one or more of the assumptions outlined above may not be justified; for example, when there are wide fluctuations from the steady state. Serum TSH values frequently are subnormal in the absence of thyrotoxicosis and serum free T4 estimates are subject to multiple interfering influences, depending often on the particular method. Dual assessment clearly is necessary to identify the serum free T4 TSH combinations that indicate true thyroid dysfunction. When a patient has both thyroid dysfunction and a severe nonthyroidal illness, assessment becomes especially difficult because the effects of the illness, medications, or changes in nutrition can alter the expected changes in serum free T4 or TSH. Only clinical re-evaluation and repeated sampling may resolve the dilemma.

Thyroid Diagnosis and Treatment

There are three general principles upon which the physician should focus when evaluating thyroid function in a patient. These principles are: The thyroid gland is the principal site of thyroid dysfunction. Autoimmune thyroid disease is the most common aetiology producing the dysfunction. Thyroid status is best determined by a combined measurement employing a serum free thyroxine (FT4) estimate and thyrotrophin (TSH). For both hypothyroidism and hyperthyroidism, TSH and an estimate of free T4 (FT4) are recommended. T3 or free T3 may be needed to confirm hyperthyroidism if free T4 is within limits. Anti-thyroid antibodies, preferably antithyroid peroxidase (anti-TPO), may establish an autoimmune mechanism.

Recommendations for Thyroid Testing

Hyperthyroid

Symptomatic	Free T4, TSH
Post-therapy	Free T4 (Free T3)

Hypothyroid

Symptomatic	TSH, Free T4 (anti-TPO)
Subclinical	TSH-first (T4, anti-TPO)
Monitor replacement	TSH
Hypopituitary	TSH and Free T4
Acutely Ill	None without suspicion

Pregnant

Diagnosis	TSH, Free T4
Hypo, treated	TSH

Elderly

Healthy	None
Ill	None
Women > 60 years	TSH
High risk*	TSH
Healthy adults	None without suspicion

*Ambigious symptoms, concurrent illness associated with thyroid disease, drugs associated with thyroid dysfunction.

Diagnostic Approach to Anomalous Serum T3, T4, and TSH Values

Clinical re-evaluation, with particular attention to long-term features suggestive of thyroid disease and to the medication history. Measurement of serum TSH by a third generation method to identify conclusively the degree of TSH suppression. Measurement of the serum T3 concentration with appropriate binding correction (free T3). An authentic estimate of serum free T4 (particularly in euthyroid hyperthyroxinaemia). Follow-up to establish whether the abnormality is transient or persistent. Search for evidence of unusual binding abnormalities or hormone resistance in the propositus and family members.

Typical Reference Ranges for Serum Thyroid Hormones and TSH in Humans*

Hormone	Reference ranges	Variations unrelated to thyroid disease
Total T3	69-202 ng/dl	Binding protein changes, binding competitors, age-related changes, nutrition, illness, surgery, drugs
Free T3	1.4-4.2 pg/ml	Methodologic factors and influences on total T3
Total T4	4.4-11.6 µg/dl	Binding protein changes, binding competitors
Free T4	0.8-2.0 ng/dl	Methodologic factors, pregnancy
TSH	0.28-6.82 µIU/ml	Diurnal variation, pulse secretion, age-related changes, drugs

*These ranges should be determined for the particular methods used in each laboratory. The neonatal period is excluded. Higher values in childhood.

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